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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/764,918	GYURIS ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27,34,49-52 and 63-77* is/are pending in the application.

4a) Of the above claim(s) *7 and 9-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,12-27,34,49-52,and 63-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *3/24/04*, 3129104
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/10/2003, 4/14/2003, and 3/30/2004 has been entered.

RCE filed on 10/10/2003 instructed the Office to enter Amendment filed on 06/13/2003. However, the Office could not locate the amendment and applicant was asked during the Examiner-initiated interview (see the attached interview summary conducted on March 23, 2004) whether an amendment was filed on 6/13/2003. Applicant stated that an amendment on 06/13/2003 was not filed and applicant instructed (during the same interview) the Office to enter the after-final amendment filed on 4/14/2003.

During the Examiner-initiated interview (see the attached interview summary conducted on March 29, 2004), applicant was requested to provide a complete listing of all the claims following the new amendment procedure because the prosecution history indicates that there appears to be discrepancy between the Office's record and the applicant's record about which claims are pending and what claims are misnumbered. In response to the interview, applicant submitted, on 30 March 2004, the listing of

claims with the instruction that "the following listing of claims replaces all previous versions of the claims:"

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

This Office action contains new grounds of rejection.

Election/Restrictions

Claims 1-27, 34, 49-52, and 63-77 are pending. Claims 1-6, 8, 12-27, 34, 49-52, and 63-77 are being examined as to the extent they are drawn to the elected Species B of tyrosine kinase receptor (note the Office action mailed on 11/16/2001, and applicant's response filed on 1/8/2002 at page 7), while claims 7, and 9-11 **remain withdrawn** from examination as being drawn to a non-elected species for reason of record.

Claim Rejections - 35 USC § 102

Claims 1-4, 6, 8, 12-27, and 34 remain rejected, and claims 49-52, and 63-77 are newly under 35 U.S.C. 102(b) as being anticipated by WO 95/30759 (Publication date Nov. 6, 1995, IDS AB filed on July 5, 2002, Paper No. 13) as evidenced by Fixe et al., of record (1998, Cytokine vol. 10, pages 32-7, the full article provided with this Office action).

Claims 1-4, 6, 8, 12-27, 34, 49-52, and 63-77 are interpreted as drawn to a chimeric polypeptide comprising a serum albumin (SA) with a useful heterologous peptide inserted anywhere into said serum albumin (claims 1, 63), inserted in the middle of SA (claims 2, 3, 64, and 65), wherein the chimeric polypeptide exhibits increased biological activity relative to the heterologous peptide sequence itself (base claims 1-3),

the chimeric polypeptide binds to a tyrosine kinase receptor (elected species) under physiologic conditions (base claims 63-65), wherein the heterologous peptide is derived from an angiogenesis-inhibiting proteins (claims 4, 69), from a protein or peptide fragments that binds to a tyrosine receptor i.e. the elected species (claims 6, and 8), wherein the chimeric polypeptide binds to said receptor (claims 12, 66), is an agonist (claim 13), or antagonist (claim 14) of said receptor, induces apoptosis (claims 15 and 67), modulates cell proliferation or differentiation (claims 16, 17, and 68), wherein the size of the heterologous peptide inserted could be anywhere from 4 to 400 amino acids (claims 18-21, and 70), wherein the tertiary structure of the chimeric polypeptide is similar to native serum albumin (claims 22, and 71), wherein the inserted peptide sequence replaces a portion of a native SA (claims 23, and 72), wherein the inserted sequences and replaced portion of native SA sequence are unequal length (claims 24, 73), wherein the half-life of the chimeric polypeptide is no less than 14, or 10 days, or no less than 50% of the half-life of native SA (claims 25-27), wherein a pharmaceutical composition comprising the chimeric polypeptide is claimed (claim 34), wherein a cysteine loop, or several specific cysteine loops are recited in claims 49-52, and 74-77 as an insertion site in SA.

Applicant in the response filed on 04/14/2003 argues that instantly claimed invention is directed to a chimeric SA polypeptide that "exhibits increased biological activity to the heterologous peptide sequence itself (emphasis added)"; WO 95/30759 is completely silent about increased biological activity, but merely hopes that a chimeric polypeptide may possess enhanced stability; enhanced stability is still different from

increased biological activity. These arguments have been fully considered but they are not persuasive because a review of the prosecution history indicates that applicant had argued that an increased half-life in vivo is an increased biological activity. See page 13-17 of Paper No. filed on 07/05/2002. Therefore, the 759 patent that teaches increased in vivo half-life of a heterologous peptide when inserted into a SA, is an art for the instantly claimed invention. Further, the instant application as originally filed does not disclose that enhanced stability and increased biological activity are different. Thus, it is concluded that applicant is arguing with a definition not present in the application as originally filed.

Applicant argues that SA undergoes N-F transitions, and the '759 patent is limited to a heterologous peptide inserted in SA can serve as a substrate for protease cleavage under non-physiologic in vitro conditions, which is about 10-times more than normal physiologic conditions; the '759 patent fails to describe any assay or even comparing biological activities, no less potencies, due to factors such as conformation in a specific solution, whereas the instant specification at page 41, paragraph 1 teaches one example, a synthetic EC binding peptide inserted into mouse serum albumin has 1000-fold higher biological activity than the synthetic binding peptide alone. These arguments have been fully considered but found unpersuasive because applicant argues with limitations not in the claims. The instant claims do not have any limitation concerning an assay comparing potencies of biological activities due to factors such as conformation in a specific pH solution. The application as originally filed does not disclose the invention is limited to chimeric SA as the applicant now argues. Further,

the instant claims are not limited to the particular chimeric SA polypeptide structure disclosed at page 41, therefore arguing with one particular strucutre is seen as an argument not commensurate in scope of the claims.

Further, the RGD sequence used as the control in the assay at page 40 is a cyclied RGD peptide (note 2nd paragrph under the heading "BCE Proliferation Assays), whereas the RGD sequence inserted in MSA is a linear peptide. This conclusion is made because the specificaiton does not teach how to insert a cyclic RGD sequence directly into a SA. The instant application at pages 12-13 discloses that making the claimed chimeric polypeptide could be complished using the art-known recombinant DNA technology. Thus, comparison of a cyclic RGD vs. a linear RGD in SA do not seem to fit the description of the limitation "a serum albumin (SA) having **a biologically acitve heterologus peptide seqeunce** inserted therein, wherein the chimeric polypeptide exhibits increased biological activity relative to **the heterologous peptide sequence** itself", because the claims 1-3 compare a linear peptide to said linear peptide inserted in SA. Note the first mentioned heterologus peptide and the second mentioned heterologus peptide in claims 1-3 should be same. However, the 1000-fold inreased activity is comparing a cyclic peptide with a linear peptide in SA. Therefore, the argument with the RGD sequence is considered with arguing a limitation not present in the claims.

Applicant further argues that the '759 patent fails to anticipate the new claims directed to chimeric polypeptide that bind cell surface receptors under physiologic conditions; the '759 patent is not even enabled for chimeric polypeptide that bind cell

surface receptor because serum albumin undergoes conformmational changes in a different pH, the pH at page 30 of the '759 patent is not physiological conditions, thus the '759 patent is not enabling disclosure for the instantly claimed invention, therefore not art. These arguments have also been fully considered but found not persuasive because the '759 patent discloses that **pharmaceutical compositions** comprising a heterologous peptide or protein capable of binding to a tyrosine kinase (M-CSF) recetor; this pharmaceutical would inherently bind to a tyrosine receptor in vivo. Pharmaceutical compositions recited in claim 25 of the '759 patent are used under physiological conditions because inherent in "pharmaceutical" is in vivo use. The '759 patent teaches all the necessary DNA recombinant technology and other steps for example, protein expression in yeast to make the instantly claimed chimeric SA polypeptide. The strucutre claimed in the instant claims and the structure disclosed in the '759 are same, therefore, the chimeric SA polypeptide of the '759 patent inherently has all the functional properties. See below for further detail on what the '759 patent teaches:

WO 95/30759 teaches a chimeric polypeptide comprising a serum albumin having a biologically active heterologous peptide ("the biologically active peptide" at page 7 line 16 is used in context of the inserted peptide, thus it is heterologous) inserted preferably in exposed loops of a serum albumin for purpose of increasing the half-life of said biologically active heterologous peptide. Note pages 8 and 9 for the advantage of using SA as a carrier protein for a pharmaceutical preparation. Based on the crystal structure solved by He and Carter of record (1992), the '759 teaches that one of the preferred insertion site (an exposed loop) lies in residues 57-62 of human SA (note

page 7, line 7), which is a portion of a cysteine loop claimed instant claims 49-52, and 74-77.

The '759 patent at Fig. 2 and pages 7-8 discloses that the inserted sequences and replaced portion of native SA sequence are unequal length, the inserted peptide sequence replaces a portion of a native SA. This teaching anticipates instant claims 23, 24, 72, and 73.

The '759 patent teaches at page 1 that chimeric human serum albumin with a therapeutically useful heterologous peptide inserted presents said useful heterologous peptide at its sites of interaction, and assures a high plasma stability, and said therapeutically useful heterologous peptide could be derived from various therapeutically useful protein including an angiogenesis-inhibiting proteins (see "tumoral angiogenesis" at page 4 line 9), from a protein or peptide fragments that binds to a tyrosine kinase receptor (see below that M-CSF is a tyrosine kinase), or antagonist or agonist peptide sequence (note pages 3-4) with various in vivo functional properties. This teaching anticipates the various of functional properties of either the heterologous peptide or the chimeric SA polypeptide recited in instant claims 4, 6, 8, 12-17, and 66-69. Since instant specification at page 6 discloses that it is known in the art that SA does not have any activity, any resulting activity of the chimeric SA is due to the inherent activity of the inserted heterologous peptide.

The '759 patent teaches at page 6, lines 3-6 that the size of peptide inserted could range 1-100 residues. This teaching anticipates the limitation of instant claims 18-21, and 70.

The '759 patent teaches at page 6 lines 11-13 that structure of the albumin cannot undergo too much destabilization. This teaching is seen as anticipating the limitation of instant claims 22 and 71 because the claimed structure and the structure of the prior art appear to be same i.e. the overall structure of chimeric SA should be similar.

Although the '759 patent does not specifically teach the half-life of the chimeric polypeptide is no less than 14 or 10 days, or no less than 50% of the half-life of native SA (claims 25-27), it is the Office's position that the structure of instantly claimed chimeric SA and the structure of the chimeric SA taught by the prior art is same, therefore the recited specific half-life is the inherent property of the chimeric SA of the prior art.

Since applicant elected a tyrosine kinase receptor as species, the Office will elaborate on this aspect in detail. Although WO 95/30759 does not specify the functional properties of the various therapeutically useful proteins and peptides, the functional properties of the various therapeutically useful proteins or peptides listed at pages 3 and 4, and claim 3 of the '759 patent are inherent properties of the various therapeutically useful proteins or peptides.

Fixe et al., of record (1998, Cytokine vol. 32-7, a fully copy provided with this Office action) present evidence. It is well known in the art before the effective filing date of the instant application that M-CSF is a tyrosine kinase receptor. Thus, a biologically active recombinant polypeptide essentially consisting of at least one active portion derived from M-CSF (see line 7 from the bottom of page 3 of the '759) inserted into SA

would bind to a tyrosine kinase receptor protein (i.e., M-CSF-R), and to an extracellular domain of M-CSF-R.

Any rejection set forth in the Office action mailed on 12/13/2002, but not repeated here in this Office action under 102 (b) is withdrawn.

Claim Rejections - 35 USC § 103, Withdrawn

The rejection of claims 49-52, and 75-77 under 35 U.S.C. 103(a) as being unpatentable over WO 95/30759 (Publication date Nov. 6, 1995, IDS AB filed on July 5, 2002, Paper No. 13) as applied to claims 1, 23, 63 above, and further in view of Carter et al (1994, Advances in Protein Chemistry, vol. 45, pages 153-203, IDS AE filed on July 5, 2002, Paper No. 13) is **withdrawn** in view that the claims are now rejected under 102 (b) above.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 112

Claims 22, 25-27, 50, 52, 71, and 75, and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22 and 71 recite "similar" respectively, but it is not clear what the metes and bounds are.

Claim 25 recites the limitation "the half-life" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 26 recites the limitation "the half-life" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 27 recites the limitation "the half-life" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 50, 52, 75, and 77 are rejected because they recite several specific cysteine residues without any reference frame. This is reinstatement of the rejection set forth in Paragraph 3 of the Office action mailed on 4/9/2002. Applicant argued at pages 12-13 of the amendment filed on 07/05/2002 that the drawing part of the specification illustrates the 3-D space-filling model of human serum albumin; Figures 4A-4I illustrate the position (on the 3-D model) of the claimed cysteine loop regions of mouse serum albumin aground the Cys53-Cys62 loop, with Cys53 and Cys62 marked in bold; the protein sequences of the highly conserved human and mouse serum albumin are well known in the art before the filing of the instant application as evidenced by the GenBank entry shown in Exhibit A; thus, in both human and mouse serum albumins, residues 53, 62, 75, 91, 90, 101, 245, 253, 266, 279, 360, 369, 461, 477, 476, 487, 558, 567 are all known to be cysteins, therefore the instant application unequivocally provides unique identification for amino acid positions recited in the claims. This argument has been fully considered but not persuasive for following reasons.

The scope of the claimed invention is not limited to human or mouse serum albumin but the instant application at page 9, the third paragraph defines the limitation serum albumin as "intended to include (but not necessarily to be restricted to) serum albumin proteins of living organisms, preferably mammalian serum albumins, even more preferably known or yet-to-be-discovered polymorphic forms of human serum albumin (HSA), and variants thereof." Claim 50 depends on claim 47, which in turn depends on

claim 1. Serum albumin of claim 1 is not limited to human or mouse known serum albumin sequences. However, the specification does not reasonably teach which amino acids of a serum albumin sequence is a reference sequence.

Carter and He (IDS AE filed on 6/05/2002, 1994, Advanced in Protein Chemistry 45, pages 153-203) at page 160, lines 4-9 teach that there are more than one nomenclatures being used for various serum albumins and the authors of the review articles define that the residue designation of serum albumin is normalized to HSA (human serum albumin). Peter, T (1985, Adv Protein Chem. vol. 37, pages 161-245) at Figs. 1 and 2 (page 168-170) teaches that bovine serum albumin is shorter than the human serum albumin by three amino acids, two of the three lie in what is commonly known as cysteine loop 3 (see Fig. 2). Thus, human serum albumin Cys360-Cys369 correspond to bovine Cys358-Cys367. Therefore, one would have difficulty to determine whether inserting a biologically active peptide into the bovine Cys358-Cys367 would infringe on the instantly claimed invention. Even if the instantly recited cysteine loops refer to a mature human and mouse serum albumin protein sequences, applicant's terminology in the instant specification is not consistent with that of art because Peter, T (cited) above teaches that the mature human serum albumin does not have cysteine residues at amino acid #266 as indicated in claims 50, 52, 75, and 77, but amino acids #266 is glutamic acid (E). The specification does not disclose that the instant applicant discovered a new human serum albumin with a cysteine residue at #266.

Claims 1-6, 8, 12-27, 34, 49-53, and 63-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

This new matter rejection is made because of the added limitation claims 1-3 with the amendment on 01/08/2002, and also the limitation "under physiological conditions" in the new claims 63-65. All claims that depend on the rejected base claims 1-3, and 63-65 are also rejected.

First, claims 1-3 have the limitation "wherein the chimeric polypeptide exhibits increased biological activity relative to the heterologous peptide sequence itself." This limitation was added with the amendment filed on 01/08/2002. At page 6, the first paragraph of the amendment, applicant stated that the support for the subject matter of the amended claims 1-3 can be found throughout the specification, for example, page 41, first paragraph. However, the specification at page 41, first paragraph discloses when a specific RGD binding peptide is inserted into a specific location of mouse serum albumin (MSA), the resulting chimeric RGD-MSA has approximately 1000-fold inhibitory activity to cells in vitro as compared to the cyclic RGD. Note bottom half of page 40 for BCE proliferation assays under the Heading "BCE Proliferation Assays" and the construction of the chimeric polypeptide at page 39.

The support applicant specifically pointed out in the specification as originally filed is not same as the limitation in the instant claims 1-3 i.e. "wherein the chimeric polypeptide exhibits increased biological activity relative to the heterologous peptide sequence itself", because the scope encompassed by the limitation is broader than the support at the first paragraph of page 41.

Applicant is kindly requested to point out the support for the limitation in the application as originally filed because the support is not apparent to the Office.

Second, the new claims 63-65 have the limitation "under physiological conditions". At page 9, second paragraph of the amendment filed on 04/14/2003 states that the limitation is implicitly supported by the specification since the specification teaches culturing of EC cells in vitro, "which closely proximates physiological growth conditions *in vivo*." However, the specification at page 40, under the heading "BCE Proliferation Assays" discloses that the bovine capillary EC cells at passage 11 were plated in 5% calf serum/DMEM supplemented with penicillin/streptomycin in an atmosphere of 10 % CO_2, 37 °C, followed by media change to 2% calf serum on day one before adding either the chimeric polypeptide or a synthetic cyclic RGD. The application as originally filed does not define what is "physiological conditions". The application as originally filed does not define "under physiological conditions" is the same as the in vitro conditions set forth at page 40. Merriam Online Dictionary downloaded from url..m-w.com on 6/9/2004 defines that "physiology" as a branch of biology that deals with the functions and activities of life or of living matter. Thus, "under

physiological conditions" is interpreted as in vivo conditions as compared to in vitro conditions based on the definition stated in the dictionary.

Here again, "under physiological conditions" is broader in scope than the in vitro conditions set forth at page 40 of the specification because "under physiological conditions" could include many different in vivo criteria. For example, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been

in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Roy et al., (2003, Circulation Research. Vol. 92, 264) teach that cellular O_2 concentrations are maintained within a narrow range (normoxia) because of the risk of oxidative damage from excess O_2 (hyperoxia) and of metabolic demise from insufficient O_2 (hypoxia). The ambient PO_2 in vitro culture conditions is much higher than in vivo physiological conditions, causing inhibition of cell growth. Note pages 264-265, and Fig. 1. Thus, "under physiological conditions" also include a correct oxygen pressure.

Thus, "under physiological conditions" include nervous and endocrine input, cell to cell interactions, a correct oxygen pressure, etc.

The scope of the limitation "under physiological conditions" in the newly present claims 63-65 is broader than the disclosure in the EC in vitro cell culture conditions in the specification, therefore it is new matter. In fact, the EC in vitro cell culture conditions with the high antibiotic concentrations and the high bovine serum albumin concentrations do not appear to be "under physiological conditions" for human cells in vivo.

Claims 1-6, 8, 12-27, 34, 49-53, and 63-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the exposed regions of a serum album as insertion sites, does not reasonably provide enablement for the buried

regions of a serum albumin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

This rejection is made because the claimed invention is interpreted as drawn to a chimeric polypeptide comprising a chimeric serum albumin with an inserted biologically heterologous peptide buried in said serum albumin.

The specification at page 37 discloses that when a heterologous peptide inserted in SA at residues 467-468 (a middle of one of the recited cysteine residue in claim 50, for example), the inserted heterologous peptide is buried and therefore inaccessible. The specification does not teach how to use the buried heterologous peptide in a chimeric SA polypeptide. When the heterologous peptide is buried in a chimeric SA polypeptide, it does not appear to exert its biological activity in any conditions. WO 95/30759 (AB of IDS filed on 06/05/2002, Paper No. 14, publication date: 11/16/1995) at page 6 teaches that one critical element for chimeric serum albumin is accessibility of the inserted heterologous peptide.

Considering the unpredictable state of art, limited guidance, no examples in the specification how to use a chimeric SA with a buried heterologous peptide in said SA, and broad breath of the claims, it is concluded that undue experimentation is required to practice the full scope of the invention.

Claim Rejections - 35 USC § 103

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/30759 (cited above) in view of Zetter (1998, Annu Rev Med. Vol. 49, pages 407-24, the fully article provided with this Office action).

Claims 1-5 are interpreted as drawn to a chimeric polypeptide having an anigostatin or endostatin inserted in a serum albumin (SA).

As stated above, the '759 patent teaches that a therapeutically useful peptide such an angiogenesis-inhibiting protein could be inserted into a SA such that the resulting chimeric SA polypeptide has higher in vivo half-life and other clinically beneficial properties. Note "tumoral angiogenesis" at page 4 line 9 and page 8 for advantage of inserting a therapeutically useful peptide in a SA.

The '759 patent does not specifically teach "anigostatin" or "endostatin".

However, Zetter of record (1998, Annu Rev Med. Vol. 49, pages 407-24, the full article provided with this Office action) teaches at page 414-5 that both angiostatin and endostatin are angiogenesis inhibiting proteins, and both are proven to be useful in treating cancer in vivo.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the claimed invention was made to make and use the claimed

chimeric SA having either angiostatin or endostatin as the biologically active heterologous peptide with a reasonable expectation of success given the detailed teaching of how to make a chimeric SA at pages 9-30 of the '759 patent and also given the teaching of Zetter that angiostatin and endostatin are known before the effective filing date of the instant application. Further, Zetter teaches that those two angiogenesis inhibiting proteins are proven to be effective in vivo. Therefore, one of ordinary skill in the art would be motivated to make and use the instantly claimed product since the '759 patent teaches at pages 8 and 9 that the chimeric SA polypeptide will reduce the dosages administered, thus reduce side effect associated with administering a large dosage, and also because Zetter teaches that either angiostatin or endostatin has been proven to be effective in vivo cancer treatment.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina C Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642